1. **The Claimed Invention Meets the Requirements Under 35 U.S.C. § 112**

The Applicants Were In Possession Of The Invention As Claimed At The Time The Application Was Filed

Claims 1-5, 20-22 and 28-29 drawn to a recombinant influenza viral genome encoding a tumor-associated antigen and vaccine formulations, are rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The rejection is in error and the Applicants respectfully submit that the invention as claimed in claims 1-5, 20-22 and 28-29 is enabled by the instant disclosure so as to convey to a skilled artisan the fact that the inventors were, indeed, in possession of the invention.

The instant specification meets the written description requirement of 35 U.S.C. §112, such that a skilled artisan would realize the Applicants were in possession of the invention as claimed. The invention as claimed relates to genetically engineered recombinant influenza viruses that express tumor-associated antigens ("TAAs"). The specification teaches and it is routine in the art to engineer influenza viruses. As one example of a method to engineer recombinant influenza viruses, the instant specification cites to and incorporates by reference U.S. Patent No. 5,166,057 and PCT Publication No. WO 93/21306, which provide ample disclosure to allow one skilled in the art to engineer recombinant influenza virus which contain TAAs. (See, the instant specification at pages 8 and 26; pp 15-17 of the specification, and references cited therein). Examples of specific tumor antigens are provided by the instant specification (see pages 8-10 of the specification). The characterization of all of these antigens is well known in the art, including the amino acid sequence of the peptide which is

presented to the cytotoxic T cells (see Boon et al., 1995, *Immunol. Today* 16:334; Estin et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:1052; Robbins et al., 1996, *Current Opinion in Immunology* 85(5):628 and 629). Furthermore, the instant application coupled with the state of the art at the time of filing, provides assays to determine whether or not the recombinant influenza virus containing a TAA elicits a T cell response, in addition to providing an animal model to determine the efficacy of the of the recombinant virus. (See pages 15 to 22 of the instant specification). Thus, the instant specification coupled with the state of the art as of the filing date of the instant application does indeed reasonably convey to one of skill in the art that Applicants were in possession of the claimed invention. Accordingly, Applicants submit that the written description requirement of 35 U.S.C. §112 has been fully met.

The Examiner mistakenly relies on *Fiers v. Sugano*, 25 USPQ2d 1601-1607 (CAFC 1993) to support the position that the instant invention has allegedly not been reduced to practice. *Fiers* involved an invention relating to nucleic acids encoding a novel gene. In *Fiers* the court held that in the absence of isolating the nucleic acid encoding the gene or a definition of its structure, reduction to practice had not occurred. In the instant case, the claimed invention relates to recombinant influenza viruses engineered to contain a tumor associated antigen which elicit a cytotoxic T cell response. The specification teaches and it is routine in the art to engineer influenza viruses to contain heterologous sequences. The specification provides a laundry list of tumor associated antigens, the structure of which were known at the time the application was filed, which may be selected to be engineered into the influenza viruses. Furthermore, the specification teaches and as of the filing date of the instant application, it was routine in the art to assay the recombinant viruses containing TAAs to determine if a cytotoxic T cell response will be elicited. Thus, unlike *Fiers* the structure

of the claimed recombinant viruses is provided by the instant specification and there can be no question that the invention has been reduced to practice.

The Instant Specification Enables The Full Scope Of The Invention As Claimed

Claims 1-5, 20-22 and 28-29 are rejected as the specification allegedly does not contain sufficient written description to enable the full scope of the invention as claimed. The rejection is in error and as discussed below, Applicants assert that the specification fully describes the claimed invention and, coupled with the state of the art at the time the specification was first filed, enables one of skill in the art to make and use the claimed invention without having to resort to undue experimentation.

Claims 1-5, 20-22 and 28-29 are drawn to a recombinant influenza virus that encodes a tumor associated antigen within its genome. The instant specification meets the requirement of the first paragraph of 35 U.S.C. §112 by providing an adequate written description of the invention as claimed.

The instant specification teaches how to make a recombinant influenza virus using, for example, the techniques of reverse genetics (see the instant specification at pp. 7-9). The instant specification provides a detailed description regarding the construction and use of a recombinant influenza virus expressing a model tumor antigen (see the instant specification at pp. 15-20). The specification also describes, in detail, assays which may be used to characterize the immune response generated by a recombinant influenza virus encoding a tumor associated antigen (see the instant specification at p. 18). Further, the specification teaches that the recombinant influenza virus expressing a model tumor antigen is effective at reducing tumor metastases in an animal model (see the instant specification at pp. 19-24).

Additionally a list of known tumor associated antigens is provided in the specification (see the instant specification at p. 8). Any one of these tumor antigens could be readily engineered, by a skilled artisan, into a recombinant influenza virus using the methods provided in the specification. Hence, the invention as claimed is fully disclosed in a written description, and when combined with the state of the art at the time of filing, would permit a skilled artisan to practice the invention as claimed.

The instant specification meets the legal test for enablement. The Examiner cites *In re Wands*, 8 USPQ 546 (PTO Bd. Pat. App. Int., 1986) for the legal considerations regarding enablement. The Examiner should note that this case was overturned on appeal to Federal Circuit Court of Appeals. (See *In re Wands*, 858 F2d 731 (Fed. Cir. 1988). In its decision, the Federal Circuit Court of Appeals stated:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The disclosure is objected to for failing to provide adequate guidance regarding the invention as claimed. It is alleged that while the claims broadly encompass any tumor associated antigen, only the sequence of the β-gal antigen is disclosed hence a skilled artisan could not predict the nucleotide sequence necessary to generate an immune response against a given tumor antigen. This allegation is in error. Any experimentation required to practice the invention is indeed routine and the art provides adequate guidance regarding the identification of suitable tumor associated antigens and their epitopes which may be engineered into a recombinant influenza virus. The art also teaches methods for discovering new tumor

Not Routine

associated antigens. Hence, the objection regarding the ability of a skilled artisan to practice the invention given the matter disclosed in the specification is in error.

The characterization of tumor associated antigens is well known in the art (Boon et al. 1995, *supra* 16:334; Estin et al. 1988, *supra*;) and more importantly the actual peptide sequence, derived from many tumor antigens, required to elicit a cellular immune response, is known in the art and was known as of the filing of the instant application (Robbins et al. 1996, *supra*). Given the peptide sequence, the skilled artisan could readily deduce the nucleotide sequence and combined with, for example, the reverse genetics technique disclosed in the instant specification could merely cut and paste the appropriate sequences into the recombinant influenza virus.

β-gal is merely disclosed as an illustrative example of the technology. The Applicants are not required to disclose every conceivable example. (See *Amigen Inc. v. Cugai Pharmaceutical Co. Ltd.* 927 F. 2d 1200 (Fed. Cir. 1991)). Thus, with regard to the requisite sequences of tumor associated antigens, the specification combined with knowledge in the art provide adequate guidance to practice the invention and hence the breadth of the claimed invention is adequately supported by the disclosure.

The specification is objected to for failure to provide structural motifs common to tumor associated antigens. This objection is in error. The common structural motifs for generating a cellular immune response for any antigen are known in the art. These structural motifs include the proper peptide length and the appropriate anchoring sequences to bind the peptide in the MHC I groove. (*see* Boon et al. *supra*. Van Pel et. al *supra*.)

It is alleged that the disclosure fails to include a clear, concise and reproducible method for obtaining tumor associated antigens with the desired activity commensurate in scope with

that which is claimed. This allegation is in error. The specification discloses, for example, the technique of reverse genetics which can be used to engineer recombinant influenza virus to express a heterologous epitope, including a tumor antigen. The technique is described clearly and concisely (See U.S. Patent No. 5,166,057; PCT Publication WO93/21306; Enami et al. 1991, *J. Virol.* 65:2711). The instant specification provides working examples (pp15-26 of the specification) that describe the construction, characterization, and *in vivo* efficacy in the context of cancer immuno-therapy of recombinant influenza virus vectors expressing a model tumor antigen.

The art teaches how peptide sequences, which are capable of eliciting a cellular immune response, and which are derived from tumor associated antigens can be identified (*see e.g.* Van Pel et. al 1995 *Immunol. Rev.* 145:229; Robbins et al. 1994 *Cancer Res.* 54:3124; Wang et al. 1995 *J. of Exp. Med.* 181:799).

The teachings of the specification when combined with the knowledge in the art do in fact provide a clear, concise, reproducible method for obtaining any tumor associated antigen with the desired activity and engineering that antigen into a recombinant influenza viral vector. The mere fact that there are many potential tumor antigens does not preclude enablement, provided that there is adequate disclosure in the specification and the art to permit the skilled artisan to practice the invention. This is true even if a considerable amount of laborious experimentation is required (*see In re Wands, supra.*).

It is alleged that the prior art is unpredictable. This allegation is in error. As discussed above the prior art teaches the identification of tumor associated antigens. It teaches the identification of peptide sequences derived from tumor antigens necessary to elicit a cellular immune response. The art also teaches methods to identify new tumor associated antigens.

Hence the art is not unpredictable. The Examiner cites Rao et al., (1996, *J. Immunol.* 156:3357) and Restifo et al. (1996, *Current Opin. in Immunology* 8:658) to support the position that the art of cancer immuno-therapy is unpredictable. Reliance on these two articles to support unpredictability in the art is, however, misplaced.

Rao suggests that the use of β-gal as a model tumor antigen may be inappropriate because it is a large xenogeneic antigen likely to elicit a strong immune response on its own. The implication is that, in effect, by using such a seemingly strong immunogen - the deck is being stacked in favor of a strong immune response against the tumor. But, Rao's primary concern turns out to be unfounded because as Rao states in the quotation cited by the examiner they saw no evidence of a systemic immune response directed against β-gal. Based upon Rao's own findings, the conclusion that must be reached is that β-gal is a good model for tumor antigens.

Rao also hypothesizes that β-gal is most appropriate as a model for tumor antigens resulting from viruses . . . or genetic events that result in expression of foreign proteins arising from mutations, however, provides no data to support this hypothesis. Nonetheless, contrary to the Examiner's position, many of the tumor antigens cited in the instant specification are derived from the expression of foreign proteins arising from mutations or from viruses.

Restifo argues that the use of the CT26.WT and CT25.CI25, highly aggressive tumors, may be an inappropriate model for human cancers because in comparison, human cancers grow much more slowly. Restifo provides no data to support this position. Furthermore, as the recombinant influenza virus expressing TAAs of the invention demonstrated *in vivo* efficacy against these highly aggressive tumors, as Applicants have demonstrated in the

instant specification, this suggests that the recombinant influenza virus of the invention would work even better against a much slower growing human cancer.

Restifo also discusses the problem of escape mutants *i.e.* tumors that escape immune surveillance. While it is true that escape mutants can occur for a variety of reasons, such as antigen loss resulting from loss of β-2 microglobulin or HLA class I, it is also true that a vigorous immune response can compensate for most escape mutants. This can be achieved by stimulating a non-specific NK cell response and by simultaneously immunizing against several antigens (see Boon et al., 1995, *Immun. Today* 16(7) at 335). Recombinant influenza viral vectors would be an ideal method to immunize against multiple antigens because of the diversity of serotypes that result from mutations in the influenza envelope glycoproteins.

For all of the reasons stated above the Applicants respectfully submit that the present invention is fully enabled and meets all of the requirements of 35 U.S.C. § 112, and request that the rejection of the claims under 35 U.S.C.§ 112 be withdrawn.

2. <u>The Withdrawal of Claims 23 to 27 Should Be Reconsidered</u>

Claims 23-27 of the instant application have been withdrawn from consideration by he Examiner as being directed to a non-elected invention pursuant to 37 C.F.R. 1.142(b) and MPEP §821.03. The withdrawal from consideration was based upon a constructive election made by the Examiner. With respect to the constructive election made by the Examiner and the reasons stated therefor, Applicants respectfully traverse and pursuant to 37 C.F.R. §1.143 requests reconsideration of the requirement.

As reasons for the restriction, the Examiner states that claims 23-27 are drawn to an invention that is independent or distinct from the invention originally claimed since said

claims specifically set forth that the respective heterologous regions encode specific tumor antigens rather than the originally claimed heterologous regions which encode tumor-associated antigens (TAA). Claims 23-37 are not drawn to an invention that is distinct or independent.

37 C.F.R. §1.141 provides that:

> (a) Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention not to exceed a reasonable number, may be specifically claimed in different claims in one national application provided that application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form (§1.75) or otherwise include all the limitations of the generic claim.

Applicants respectfully submit that claims 23-27 meet each and every requirement of 37 C.F.R. §1.141. The Examiner correctly states that claims 23-27 are drawn to **specific** tumor antigens (*i.e.*, a **species** of tumor antigens). Claim 1 is a generic claim, broadly drawn to encompass any tumor antigen (*i.e.*, a **genus** comprising tumor antigens). Dependent claims 23-27 are drawn to particular species of tumor associated antigens, which are generically covered in Claim 1. The number of species claimed does not exceed a reasonable number. Claims 23-27 claim matter that is a species of a genus claimed in claim 1. As such, claims 23-27 are properly drawn. Applicants respectfully request that the constructive restriction requirement be withdrawn and the claims be examined and allowed. The Applicants would also invite the Examiner's attention to the fact that the remaining claims, as discussed above, are rejected for failing to precisely specify the tumor-associated antigens being claimed. Hence, the Examiner has dismissed, on the one hand, claims that specify particular antigens as being drawn to an independent invention and then goes on to reject the remaining claims